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Attorney Docket No. 100390-2390
[Formerly KM39023-90]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Mosbach et al.
Serial No.	:	09/305,738
Filed	:	May 6, 1999
For	:	ARTIFICIAL ANTIBODIES, METHODS OF PRODUCING THE SAME AND USE THEREOF
Group Art Unit	:	1641
Examiner	:	Mary E. Ceperly

Assistant Commissioner for Patents
Washington, D.C. 20231

Assistant Commissioner for Patents

DECLARATION UNDER 37 C.F.R. 1.132 BY GEORGE B. SIGAL, PH.D.

Sir:

I, George B. Sigal, Ph.D., declare that:

1. I make this Declaration in connection with U.S. Application Serial No. 09/305,738, filed May 6, 1999, by Mosbach et al. entitled "ARTIFICIAL ANTIBODIES, METHODS OF PRODUCING THE SAME AND USE THEREOF" (herein "above-captioned application").

2. I am a citizen of the United States and a resident of Rockville, Maryland.

3. I am a scientist at IGEN International, Inc. in the R&D department with the title of Scientific Manager. I have been employed by IGEN since 1995. I received a Ph.D. in Organic Chemistry from Harvard University in 1996.

4. I am well acquainted through my work with the use of polymeric particles in chromatography. I have considerably experience in affinity, ion exchange and gel filtration chromatography using such resins.

5. It is my understanding that pending claims in the above-captioned application include claims 27-45 (Attached as Exhibit A).

6. I have reviewed an amended set of claims which includes claims 27-38 (Attached as Exhibit B).

7. It is also my understanding that the subject matter defined in claims 27-45 has been rejected as allegedly being unpatentable over subject matter described in U.S. Patent No. 5,100, 833 to Mosbach et al. (herein "the Mosbach reference").

8. I have read the Mosbach reference and both O'Shannessy references (D.J. O'Shannessy, B. Ekberg and K. Mosbach Anal. Biochem. 177, 144 (1989) and D.J. O'Shannessy, B. Ekberg, L.I. Andersson and K. Mosbach J Chrom. 470, 391 (1989) – I and II hereinafter) that are cited in the Mosbach reference.

9. I consider myself qualified to give the present opinions based upon my experience in chromatography and my knowledge of the subject matter defined by claims 27-45 of the above-captioned application and the subject matter described in the Mosbach reference and references cited therein.

10. It is understood in the art of chromatography that a chromatography matrix having particles of a desired size may sometimes be contaminated with smaller particles termed "fines". These fines have a tendency to clog the column and restrict the liquid phase flow. Thus, such small particulates are highly detrimental to the column packing and to the column performance. It is also understood that when column packing materials contain fines, it is highly desirable to discard the fines prior to using the material in a chromatographic column so as to ensure that there is even and efficient flow of liquids through the column.

11. The O'Shannessy references teach preparing chromatography columns using particulate molecularly imprinted material of diameter less than 25 um (i.e., materials that pass through a 25 um sieve), but only after the removal from these materials of the fines, i.e., the particles that are substantially smaller than 25 um.

12. The O'Shannessy I article teaches "Particles which passed through a 25-μm sieve were extensively defined in acetonitrile" (See, page 145). Define, in this context, would be understood by one of ordinary skill in the art of chromatography, to mean that the smaller particles in the preparation were removed and discarded. Defining is carried out by forming a slurry of particles, allowing the larger particles to settle over period of time and decanting away the particles that are too small to settle over the period of time.

13. The O'Shannessy II article also explicitly teaches the removal of fines and states that "In all cases, dust was removed by flotation in acetonitrile, and the particles were finally dried under vacuum" (See, page 393). In this case, dust would be understood by one skilled in the art of chromatography to refer to fines..

14. Like the O'Shannessy references, the present specification describes the use of molecularly imprinted polymer particles of roughly 25 um in size (Specification, page 4, lines 26-28). In stark contrast to the O'Shannessy reference, however, the present specification teaches making use of the fines in these preparations and states that "The fines ... can be kept in solution or suspension and used for instance in so-called homogenous immunoassays." (See, Specification at page 4).

15. It is my opinion that the subject matter defined by claims 27-45 of the above-captioned application is novel and non-obvious over the disclosure of the cited reference. The references do not foresee, teach or suggest the utility of the particulates of 5μm or less.

Furthermore, the O'Shannessy references teach away from the claimed size range of particles by explicitly teaching the removal of particles much smaller than 25 um prior to column packing.

16. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further, that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

By: _____
George B. Sigal, Ph.D.

Date: 10/30/03

Exhibit A

27. Artificial antibodies comprising a crosslinked polymer prepared by molecular imprint polymerization and having specific binding sites, wherein said artificial antibodies have a particle size of less than about five microns.

28. The artificial antibodies according to claim 27, wherein said particle size is between about 10 nm and 100 nm.

29. The artificial antibodies according to claim 27, wherein said specific binding sites are specific for drug molecules.

30. The artificial antibodies according to claim 29, wherein said drug molecule is theophylline.

31. The artificial antibodies according to claim 29, wherein said drug molecule is a benzodiazepine drug.

32. The artificial antibodies according to claim 29, wherein said drug molecule is diazepam.

33. The artificial antibodies according to claim 29, wherein said drug molecule has a narrow therapeutic index.

34. A method for assaying a drug molecule in a fluid, said method comprising the combination of steps:

1) providing a fluid sample with a drug molecule,

2) adding a known amount of labeled drug molecule to said sample,

3) contacting said sample of step 2) with artificial antibodies according to claim 27 so that said drug molecule and said labeled drug molecule in said sample of step 2) competitively bind with said artificial antibodies; and

4) determining the amount of said labeled drug molecule unbound in said sample or bound to said artificial antibody so as to determine the amount of said drug molecule in said fluid.

35. The method according to claim 34, wherein said labeled drug molecule includes a label selected from the group consisting of radioligands, enzymes, biotin, steroids, fluorochrome, electrochemiluminescent compounds, and gold.

36. The artificial antibodies according to claim 27, wherein said particle size is between about 10 nm and 1000 nm.

37. The artificial antibodies according to claim 34. wherein artificial antibody size is between about 10 nm and 100 nm.

38. The artificial antibodies according to claim 34, wherein artificial antibody size is between about 10 nm and 1000 nm.

39. The antibodies of claim 27, wherein said antibodies are biocompatible and have a particle size of less than about five microns.

40. The antibodies of claim 39, wherein said antibodies have a particle size in a range of from 10 nm to 1000 nm.

41. The antibodies of claim 39, wherein said antibodies have a panicle size in a range of from 10 nm to 100 nm.

42. The antibodies of claim 39, wherein said antibodies are solubilized or suspended in a liquid.

43. The antibodies of claim 42, wherein said liquid is a fluid in a mammal body.

44. The antibodies of claim 42, wherein said liquid is blood.

45. The antibodies of claim 42, wherein said liquid is blood serum.

Exhibit B

27. Artificial antibodies comprising a crosslinked polymer prepared by molecular inprint polymerization and having specific binding sites, wherein said artificial antibodies have a particle size of less than about five microns.

28. The artificial antibodies according to claim 27, wherein said particle size is between about 10 nm and 100 nm.

29. The artificial antibodies according to claim 27, wherein said specific binding sites are specific for drug molecules.

30. The artificial antibodies according to claim 29, wherein said drug molecule is theophylline.

31. The artificial antibodies according to claim 29, wherein said drug molecule is a benzodiazepine drug.

32. The artificial antibodies according to claim 29, wherein said drug molecule is diazepam.

33. The artificial antibodies according to claim 29, wherein said drug molecule has a narrow therapeutic index.

34. A method for assaying a drug molecule in a fluid, said method comprising the combination of steps:

1) providing a fluid sample with a drug molecule,

2) adding a known amount of labeled drug molecule to said sample,

3) contacting said sample of step 2) with artificial antibodies according to claim 27 so that said drug molecule and said labeled drug molecule in said sample of step 2) competitively bind with said artificial antibodies; and

4) determining the amount of said labeled drug molecule unbound in said sample or bound to said artificial antibody so as to determine the amount of said drug molecule in said fluid.

35. The method according to claim 34, wherein said labeled drug molecule includes a label selected from the group consisting of radioligands, enzymes, biotin, steroids, fluorochrome, electrochemiluminescent compounds, and gold.

36. The artificial antibodies according to claim 27, wherein said particle size is between about 10 nm and 1000 nm.

37. The method according to claim 34, wherein artificial antibody size is between about 10 nm and 100 nm.

38. The method according to claim 34, wherein artificial antibody size is between about 10 nm and 1000 nm.